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Innate Immunity

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The remarkable parallels that exist between innate immune responses to microbes in organisms as divergent as insects, fish, rodents and humans is a testament to the evolutionarily conserved nature of the ligands, receptors, and signaling pathways that orchestrate innate immunity to commensal and pathogenic microorganisms. In addition to a central role in host defense, studies in recent years have identified that dysregulated innate immunity can contribute to tissue damage, chronic inflammation and autoimmunity. The extraordinary pace of new discoveries relating to the beneficial and detrimental influences of innate immune responses is apparent in recent studies that provide new insights into the molecular mechanisms that control pattern recognition, signal transduction and expression of anti-microbial effector molecules in multiple innate immune cell lineages. In the context of these new discoveries, we are delighted to introduce ten selected reviews by colleagues that cover emerging paradigms in diverse fields of innate immunity.

Seminal studies over the last fifteen years have utilized the Drosophila system as a powerful model organism to undertake genetic analysis of innate immune recognition and anti-microbial responses. Flies are infected by a large number of viruses that exhibit remarkable diversity in their replication strategies, tropisms and pathogenesis. Many of these viral infections serve as models of human infection and disease. In this issue, **Sara Cherry and colleagues** focus on recent studies that are providing insights into novel mechanisms of anti-viral immunity in flies. The critical roles of Dicer, Ago-2 and Ars2 in regulation of RNA interference and its impact on the development of the anti-viral response are discussed. While the signaling mechanisms involved in viral immunity are being elucidated, the effector mechanisms that restrict viral infection were less well characterized. It is now clear that autophagy, a cellular process that maintains cytoplasmic homeostasis by removing toxic or redundant cellular components, can play an important role in anti-viral immunity.

John Rawls and colleagues provide an overview of the tractability of the zebrafish model for in vivo imaging and forward and reverse genetic analysis of how the innate immune system interacts with commensal and pathogenic microorganisms. The zebrafish genome encodes 24 putative variants of the TLR family, although recent studies highlight the existence of conserved and divergent functions of TLRs and their associated adapter proteins. The value of morpholino knockdown of putative effector molecules and/or lineage-specifying transcription factors is providing new insights into the importance of distinct

myeloid leukocyte populations and the NADPH oxidase system in anti-bacterial responses, while studies with germ-free zebrafish offer new insights into molecular regulation of mutualistic relationships with microbes. The emerging paradigms from studies in this vertebrate model system, including the influence of microbial challenge on hematopoiesis and angiogenesis, are also discussed.

Four reviews by **O'Neill**, **Latz**, **Eisenbarth** and **Gale** provide an overview of the recent advances that have been made by delineating the functional significance of surface, vacuolar and cytoplasmic pattern recognition receptors in innate recognition of pathogens. Until recently it was widely accepted that transmembrane receptors trigger signaling pathways almost exclusively from the plasma membrane. This view has changed radically with the discovery that receptors can signal from cytoplasmic locations. One good example is TLRs where signals emanating from the plasma membrane or endosomal organelles lead to different outcomes . **Anne McGettrick and Luke O'Neill** describe the important role played by chaperones in TLR localization. They discuss in more detail TLR4 that cycles between the Golgi and the plasma membrane until it encounters LPS. The MyD88-dependent pathway leading to NF-kB activation is initiated at the plasma membrane, followed by the trafficking of the TLR4 complex into the endosome where the MyD88-independent pathway is triggered resulting in the generation of type I interferon. Finally, proteins such as Triad3A and TAG appear to be involved in the movement of TLR4 to the lysosome for degradation. Thus, the same receptor can trigger widely different signals depending on vesicular trafficking.

Inflammasomes are molecular platforms activated upon signs of cellular ‘danger’ to trigger innate immune defenses through the maturation of pro-inflammatory cytokines such as IL-1β. Strong associations of a number of human heritable and acquired diseases with dysregulated inflammasome activity highlight the importance of inflammasomes in regulating immune responses. Since this field is in its infancy, molecular mechanisms controlling inflammasome function are still ill-defined. **Eicke Latz** reviews agonists and currently proposed activation mechanisms of the NLRP3 inflammasome. These range from a model whereby agonistic ligands are sensed by the inflammasome through a direct physical contact to an indirect activation mechanism in which products such as Reactive Oxygen Radicals induce the inflammatory response.

Eisenbarth and colleagues focus on recent developments in understanding the role of NOD-like receptors (NLRs) in recognition of pathogen-associated or danger-associated molecular patterns. NLR activation plays a critical role in assembly of the inflammasome and can influence processing and secretion of IL-1b and IL-18. Emerging studies on the influence of NLRs on adaptive immune responses have highlighted the potential utility of manipulating NLR-associated signaling in adjuvant-induced vaccination, anti-tumor immunity and treatment of autoimmune disorders.

Viral infections are detected by sensor molecules, which initiate innate antiviral responses, including the activation of type I interferons and proinflammatory cytokines. These cytokines are responsible for inhibiting viral replication. Recent advances have revealed that distinct types of sensors play a role in the detection of viral nucleic acids: TLRs detect viral DNA or RNA in endosomal compartments in immune cells; retinoic acid inducible gene-I (RIG-I)-like receptors (RLRs) recognize viral RNA in the cytoplasm; and DNA sensors detect cytoplasmic viral DNA. **Courtney Wilkins and Michael Gale** review the current knowledge of the recognition of viral nucleic acids by these sensor molecules and the signal transduction machinery employed by these pathways.

Leprosy is a chronic granulomatous disease principally affecting the skin and peripheral nervous system. It is caused by infection with *Mycobacterium leprae*. Although much improved in the last 25 years, knowledge of the pathogenesis, course, treatment, and prevention of the disease continues to evolve. Important advances include the role of PRR in recognizing pathogen associated molecular patterns of *Mycobacterium leprae* and cytokine release by innate immune cells. **Robert L. Modli**n discusses the different host responses against *Mycobacterium leprae* and the possibility to use this information in modulating the course of leprosy and other chronic infectious diseases.

Blander and colleagues discuss recent developments in understanding the molecular events that control recognition of apoptotic cells and the influence of this innate pathway on adaptive immunity. In contrast to ‘inflammatory phagocytosis’ which occurs following TLR-mediated recognition of pathogen-associated molecules, PPAR- and LXR-dependent recognition of fatty acids elicits a process of ‘non-inflammatory phagocytosis’ of apoptotic cells that appears to alter the fate of the apoptotic cell-derived cargo within phagosomes, limiting antigen presentation and inflammation. Blander and colleagues highlight that in the context of infection, integrated signals resulting from simultaneous recognition of apoptotic cells and TLR-mediated recognition of pathogens results in selective ‘transrepression’ of some inflammatory genes, resulting in a program of gene expression that influences the balance of regulatory T cell (Treg) versus T helper 17 (Th17) cell differentiation. The implications of combinatorial recognition of pathogens and apoptotic cells on immunity, inflammation and tissue repair are discussed.

The influence of microbial recognition on regulatory and inflammatory T cell responses is further discussed by **Belkaid and colleagues**. It is now well established that signals derived from microbial communities, including commensal bacteria that colonize barrier surfaces of most multicellular organisms, influence immune cell development, regulation and function. The role of defined populations of dendritic and other innate immune cells in microbial recognition and subsequent development of Treg versus Th17 cell responses is discussed in the context of murine models of infection and inflammation.

Finally, **Caroline Sokol & Ruslan Medzhitov** discuss recent discoveries on innate recognition and antigen presenting cell functions of basophils following exposure to allergens or helminth parasites. Basophils are the least common of the granulocyte lineages, representing about 0.1% of circulating leukocytes. Basophils appear in many specific kinds of inflammatory reactions and their role as effector cells of the type-2 immune response is well established. However, basophils do not only orchestrate the Th1-Th2 balance by producing critical Th2-skewing cytokines such as interleukin IL-4, but also have the capacity to act as antigen-presenting cells.

Recent years have witnessed an explosion of interest in innate immunity. Questions about how the innate immune system senses infection and metabolic problems and thereby empowers a protective immune response are being answered at the molecular level. These basic scientific discoveries are being translated into a more complete understanding of the central role that innate immunity plays in the pathogenesis of many infectious and inflammatory diseases. It is particularly exciting that we are already seeing a return on these investments with the emergence of novel therapies to harness the power of the innate immune system. Since our knowledge of the innate immune system is still limited, it is likely that further progress will be made in the next few years that will allow the development of improved therapies for the treatment of infection and inflammatory diseases.

Biography

David Artis completed his doctoral work at the University of Manchester in the UK, where he developed his research interests in host defense and immune regulation. Following completion of a Wellcome Trust Traveling Fellowship, he joined the Faculty of the University of Pennsylvania. His research focuses on host-microbial interactions in the gut and epithelial regulation of innate and adaptive immune responses at mucosal sites.

Jürg Tschopp received his PhD in biophysics at the University of Basel. He then joined the group of Müller-Eberhard at the Scripps Clinic in La Jolla working on the complement system. He was then appointed Professor at the Department of Biochemistry of the University of Lausanne. His present research focuses on signaling pathways that control apoptosis and innate immunity.